



UvA-DARE (Digital Academic Repository)

Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence

A multicentre, randomised, double-blind controlled trial

Beraha, E.M.; Salemink, E.; Goudriaan, A.E.; Bakker, A.; de Jong, D.; Smits, N.; Zwart, J.W.; van Geest, D.; Bodewits, P.; Schiphof, T.; Defourny, H.; van Tricht, M.; van den Brink, W.; Wiers, R.W.

DOI

[10.1016/j.euroneuro.2016.10.006](https://doi.org/10.1016/j.euroneuro.2016.10.006)

Publication date

2016

Document Version

Final published version

Published in

European Neuropsychopharmacology

License

Article 25fa Dutch Copyright Act

[Link to publication](#)

Citation for published version (APA):

Beraha, E. M., Salemink, E., Goudriaan, A. E., Bakker, A., de Jong, D., Smits, N., Zwart, J. W., van Geest, D., Bodewits, P., Schiphof, T., Defourny, H., van Tricht, M., van den Brink, W., & Wiers, R. W. (2016). Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: A multicentre, randomised, double-blind controlled trial. *European Neuropsychopharmacology*, 26(12), 1950-1959. <https://doi.org/10.1016/j.euroneuro.2016.10.006>

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

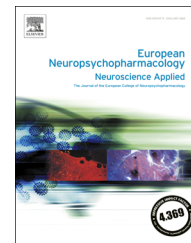
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (<https://dare.uva.nl>)



ELSEVIER

www.elsevier.com/locate/euroneuro



Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: A multicentre, randomised, double-blind controlled trial

Esther M. Beraha^a, Elske Salemink^{a,1}, Anna E. Goudriaan^{b,c,d,1}, Abraham Bakker^h, David de Jong^a, Natasha Smits^e, Jan Willem Zwart^e, Dick van Geest^f, Pieter Bodewits^g, Tom Schiphof^f, Harma Defourny^e, Mirjam van Tricht^b, Wim van den Brink^{b,c,2}, Reinout W. Wiers^{a,*,2}

^aAddiction Development and Psychopathology (ADAPT) Laboratory, Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands

^bAcademical Medical Centre (AMC), Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands

^cAmsterdam Institute for Addiction Research, Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands

^dArkin Institute for Mental Health Care, Amsterdam, The Netherlands

^eSolutionS Center, Voorthuizen, The Netherlands

^fU-Center, Epen, The Netherlands

^gThe Home Clinic, Weesp, The Netherlands

^hRoderSana Addiction Treatment, Oirschot, The Netherlands

Received 31 May 2016; received in revised form 7 October 2016; accepted 29 October 2016

KEYWORDS

Randomised placebo-controlled trial;
Alcohol dependence;
High-dose baclofen

Abstract

Previous randomised placebo-controlled trials with low-to-medium doses of baclofen (30–60 mg) showed inconsistent results, but case studies suggested a dose-response effect and positive outcomes in patients on high doses of baclofen (up to 270 mg). Its prescription was temporary permitted for the treatment of alcohol dependence (AD) in France, and baclofen is now widely prescribed. Recently, a small RCT found a strong effect of a mean dose of 180 mg baclofen. In the

*Correspondence to: Addiction Development and Psychopathology Lab, Department of Psychology, University of Amsterdam, Nieuwe Achtergracht 129B, 1018 WS Amsterdam, The Netherlands.

E-mail address: R.W.H.J.Wiers@uva.nl (R.W. Wiers).

¹Shared second authorship.

²Shared senior authorship.

<http://dx.doi.org/10.1016/j.euroneuro.2016.10.006>

0924-977X/© 2016 Elsevier B.V. and ECNP. All rights reserved.

present study the efficacy and safety of high doses of baclofen was examined in a multicentre, double-blind, placebo-controlled trial. 151 patients were randomly assigned to either six weeks titration and ten weeks high-dose baclofen ($N=58$; up to 150 mg), low-dose baclofen ($N=31$; 30 mg), or placebo ($N=62$). The primary outcome measure was time to first relapse. Nine of the 58 patients (15.5%) in the high-dose group reached 150 mg and the mean baclofen dose in this group was 93.6 mg ($SD=40.3$). No differences between the survival distributions for the three groups were found in the time to first relapse during the ten-weeks high-dose phase ($\chi^2=0.41$; $p=0.813$) or the 16-weeks complete medication period ($\chi^2=0.04$; $p=0.982$). There were frequent dose-related adverse events in terms of fatigue, sleepiness, and dry mouth. One medication related serious adverse event occurred in the high-dose baclofen group. Neither low nor high doses of baclofen were effective in the treatment of AD. Adverse events were frequent, although generally mild and transient. Therefore, large-scale prescription of baclofen for the treatment of AD seems premature and should be reconsidered.

© 2016 Elsevier B.V. and ECNP. All rights reserved.

1. Introduction

The World Health Organization (WHO) estimated that in 2012 3.3 million deaths were attributable to harmful alcohol use worldwide (WHO, 2014). In addition, harmful alcohol use is associated with more than 200 physical and mental disorders, including liver cirrhosis, cancers, injuries, and dementia, which in turn cause serious social and economic burden. The most extreme form of harmful alcohol use is alcohol dependence (AD); a chronic, frequently relapsing disorder. In Europe, about 3.5% of all drinkers meet criteria for AD (and generally high to very high drinking levels) and this subgroup of drinkers is estimated to be responsible for more than 60% of all premature (<65 years) deaths due to alcohol-attributable diseases (Rehm et al., 2013). In other words, the majority of alcohol-attributable burden is due to the relatively small group of drinkers with AD, presumably by means of heavy drinking. These numbers illustrate the importance of AD for public health and highlight the need for effective treatment. Over the past few decades, many drugs have been tested for AD treatment, but to date only disulfiram, accamprostate, and naltrexone have been approved for the indication AD by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and nalmefene is approved only by the EMA. However, although efficacy of these agents was proven in several clinical trials, other trials failed to find significant effects and the magnitude of the treatment effect was generally quite small with standardized effect sizes ranging between 0.20 and 0.40 and numbers needed to treat (NNT) ranging from 6 to 11 (van den Brink, 2012). Therefore, new effective drugs would represent an important progress in the treatment of patients with AD.

One promising drug is baclofen, a potent, stereo-selective GABA-B receptor agonist that has been used for decades in the treatment of spasticity (Davidoff, 1985). The use of drugs that act on the GABA system seems promising for the treatment of AD, because GABA-B receptors are located in the same areas of the brain as the mesolimbic dopamine neurons, which are thought to be important in the mediation of alcohol intake, reinforcement, and relapse (Koob and Volkow, 2010). Furthermore, baclofen has a low liver metabolism, and no hepatic side effects have been reported so far (Addolorato et al.,

2002, 2007). Its mechanism of action and its low abuse and dependence potential (Carter et al., 2009) makes baclofen an attractive potential drug for the treatment of AD. In rodent studies, baclofen has been found to cause reduced alcohol intake (e.g. Colombo et al., 2003). In humans, two early randomised, placebo-controlled low-dose (30 mg/day) baclofen trials in AD patients confirmed these beneficial effects (Addolorato et al., 2002, 2007), although another double blind, placebo-controlled randomised study failed to find any evidence for the efficacy of low-dose baclofen (Garbutt et al., 2010). Based on preclinical and some clinical observations, a dose-dependent effect of baclofen was hypothesized with higher doses resulting in better outcomes (Addolorato et al., 2011; Colombo et al., 2003). This hypothesis was confirmed in some case reports with baclofen doses up to 270 mg/day resulting in complete suppression of alcohol craving (Ameisen, 2005; Bucknam, 2007). Following a popular book on one of these cases (Ameisen, 2008), a French uncontrolled, open-label study reported positive effects of high dose baclofen (actual dose range: 20–330 mg/day; mean dose 147 mg/day) in 100 treatment compliant AD patients (de Beaurepaire, 2014). Based on these findings, but without data from a randomised controlled trial (RCT) on high-dose baclofen in alcohol dependent patients, a temporary recommendation of use (RTU) of baclofen was proclaimed in France in March 2014 to permit its medical prescription to AD patients for three years. Note that, even before the RTU, a significant increase of (high-dose) baclofen prescription was already observed in France: between 2007 and 2013 about 200,000 patients initiated baclofen treatment for AD and more than 9000 general practitioners were identified as first prescribers (Chaignot et al., 2015).

Recently, the first randomised controlled trial with high-dose baclofen was published: a randomised, double-blind, placebo-controlled trial on the efficacy of high-dose baclofen (up to 270 mg/day; mean dose 180 mg/day) in 56 German AD patients ($N=28$ high-dose baclofen and $N=28$ placebo; Müller et al., 2015). In this small-scale study, the overall effect was very positive (e.g., 12 weeks continuous abstinence: baclofen 68% vs. placebo 24%; $NNT=2.3$), but there was no indication of a dose-response relation. In the present trial, the efficacy and safety of low doses (30 mg/day) and high doses of baclofen (up to 150 mg/day) were examined in

a single RCT, which also allowed us to directly examine the presence of a dose-response relation.

2. Experimental procedures

2.1. Study design

The present study is a multicentre, randomised, double-blind, placebo-controlled trial. AD patients were randomised after detoxification to one of three conditions: low-dose baclofen, high-dose baclofen, or placebo. Deviant from the initial study design, the inclusion of patients in the low-dose baclofen group was stopped halfway. The trial consisted of a six-week titration phase and a ten-week high-dose phase, where the dose was stabilized.

The study protocol adhered to the principles of Good Clinical Practice and was approved by the ethics committee of the Academic Medical Centre (AMC) in Amsterdam. The study is registered at the Netherlands Trial Register, number NTR3681. Three monitoring visits took place. The trial ended when the sample size goal of the two extreme groups was reached.

2.2. Patients

Patients were recruited from two inpatient treatment centres (SolutionS Center and U-Center) and three outpatient treatment centres (The Home Clinic, Terwille, and Ready for Change) in the Netherlands. Inclusion criteria for male and female participants were: a) age between 18 and 70 years; b) DSM-IV AD-diagnosis; c) breath alcohol concentration $<0.5\%$ at the screening visit (informed consent); d) an average alcohol consumption of ≥ 14 units for women and ≥ 21 units for men per week over a consecutive 30-day period in the 90-day period before the start of the study and at least two heavy drinking days (women \geq five units; men \geq six units) in the past 90 days; e) a minimum of 96 h and a maximum of 21 days of abstinence prior to the start of the study medication; f) sufficient Dutch language skills; and g) provision of a contact person in the event of loss of contact. Exclusion criteria were a) current severe axis I disorder (other than depression, anxiety, and bipolar disorder) b) any primary diagnosis of substance dependence other than alcohol dependence (nicotine dependence was allowed); c) severe physical illnesses (e.g. Parkinson's disease, gastric ulcer, duodenal ulcer, cerebrovascular disease, respiratory insufficiency, hepatic or renal insufficiency, and epilepsy); d) anti-hypertensive medication; e) risk of suicide; f) cognitive impairment interfering with the understanding of the study; g) current or recent (three months before start of the study) pharmacological treatment for AD (i.e. acamprosate, naltrexone, disulfiram, or topiramate); h) pregnancy or breastfeeding; i) more than seven days of inpatient treatment for substance use disorder in the 30 days before the start of the study; and j) use of baclofen in the past 30 days.

All patients signed written informed consent. Patients from the inpatient treatment centres received a partial financial compensation for their treatment costs. No treatment costs and consequently no financial compensation was provided to participants from the outpatient centres.

2.3. Randomization and blinding

Patients were randomly assigned to a baclofen low-dose group (30 mg/day), a baclofen high-dose group (up to 150 mg/day), or a placebo group in a 1:1:1 ratio. Randomization (blocks of 6; pre-stratification by gender and centre) was conducted by the Clinical Research Unit of the AMC and patients were assigned to one of the three groups via an electronic database after baseline assessment but before the first

Table 1 Titration scheme during the six-week titration phase per condition.

Day	Pills per day (all conditions)	High dose Daily dose (mg)	Low dose Daily dose (mg)	Placebo Daily dose (mg)
1-7	3	30	30	0
8-10	3	30	30	0
11-12	4	40	30	0
13-14	5	50	30	0
15-17	6	60	30	0
18-19	7	70	30	0
20-21	8	80	30	0
22-24	9	90	30	0
25-26	10	100	30	0
27-28	11	110	30	0
29-31	12	120	30	0
32-33	13	130	30	0
34-35	14	140	30	0
36-112	15	150	30	0

intake of the medication. Only the study pharmacist had access to the randomization list and had no further role in the trial.

The study medication was manufactured, packaged, and labelled by Tiofarma and stored and provided by the pharmacy of the AMC. Baclofen and placebo were provided in identical 10 mg tablets and supplied in containers with 24, 42, 63, 147, or 168 tablets. Participants were supplied with medication for two weeks and pills were taken three times a day. Patients in the high-dose and low-dose baclofen group started with 30 mg/day baclofen in three gifts of 10 mg each; patients in the placebo group started with placebo. From the second week on, the dose was increased with 10 mg baclofen (for the high-dose group) or placebo (for the low-dose and placebo group) every other day, resulting in a dose increase of 30 mg/week and a maximum dose of 150 mg/day baclofen in week six in the high-dose group (see Table 1). In case of prolonged side effects, the dosage was reduced to the previous dose level and then increased again. Hence, in the high-dose group, depending on tolerance, participants could end up with a daily dosage of 30 mg, 90 mg, 120 mg, or 150 mg and continued taking this dosage during the ten-week high-dose phase. In the low-dose group, patients took a daily dosage of 30 mg for the whole study period. After 16 weeks, participants were de-blinded by an independent physician, who could suggest continuation, tapering, or cessation of the baclofen treatment in the baclofen groups or starting baclofen treatment in the placebo group. The investigators and responsible physicians remained blind with regard to the study medication during the whole study period. In the event of a relapse, patients were de-blinded and the dose was reduced with 30 mg/week, if necessary.

2.4. Procedures

In case of a positive screening, the first visit was planned for baseline measurements. During the titration phase, six weekly visits with a physician were scheduled. During the high-dose phase five bi-weekly visits or telephone visits with a psychologist were scheduled. Additionally, two test sessions were conducted four and 16 weeks after the start of the study medication. Patients from SolutionS Center followed a 28-days inpatient detoxification and treatment programme according to the Minnesota Model, whereas patients from U-Center followed a six weeks inpatient

detoxification and treatment programme based on cognitive behavioural therapy. Thereafter, these patients had weekly outpatient group sessions during the whole study period. Patients from the Home Clinic were detoxified and treated with outpatient motivational therapy and the Community Reinforcement Approach. Patients in Terwille and Ready for Change followed an outpatient detoxification and treatment programme according to the Minnesota Model. Patients in these centres had weekly outpatient group or individual therapy sessions during the whole study period.

2.5. Assessments

During the screening visit, demographic data was collected, in- and exclusion criteria were checked, and the following sections of the Mini International Neuropsychiatric Interview (M.I.N.I.) were assessed: suicide risk, anorexia nervosa, bulimia, and psychotic disorders (Sheehan et al., 1998). In the case of participation, a physical examination and the following laboratory tests were performed: gamma glutamyltransferase, aspartate amino transferase, alanine amino transferase, and carbohydrate deficient transferrin in percentage (%CDT).

At the baseline visit, the following patient characteristics were measured: severity of alcohol related problems (Alcohol Use Disorder Identification Test; AUDIT; Saunders et al., 1993), drinking history (European Addiction Severity Index; EuropASI; Blanken et al., 1994), cognitive functioning (Montreal Cognitive Assessment; MoCA; Nasreddine et al., 2005), and alcohol use in the past 30 days (Timeline Follow Back; TLFB; Sobell and Sobell, 1992). Craving (Obsessive Compulsive Drinking Scale; OCDS; Anton et al., 1995), trait anxiety (Spielberger State-Trait Inventory; STAI-trait; Spielberger, 2010), and depression (Beck's Depression Inventory; BDI; Beck et al., 1961) were assessed at baseline, after four and 16 weeks of treatment.³ At all visits during the titration and the high-dose phase, breath alcohol concentration was determined, pills were counted, adverse events were assessed with the Generic Assessment of Side Effects (GASE; Rief et al., 2009), craving was measured with the Penn Alcohol Craving Scale (PACS; Flannery, 1999), and alcohol use was assessed with the TLFB. Pill count served to assess treatment adherence. %CDT was again determined after 16 weeks as an objective measure of excessive alcohol use.

2.6. Outcomes

The primary outcome measure was time to first relapse in the high-dose phase (10 weeks) and the complete medication period (16 weeks). Following the guidelines of the German Addiction Society, relapse was defined as the first heavy drinking day (HDD), i.e. alcohol intake of more than five (females) or six (males) standard drinks per occasion, following a lapse (any alcohol intake). Similar to previous trials, it was assumed that patients who terminated the study had relapsed (Addolorato et al., 2007; Müller et al., 2015). Key secondary outcome measures were total alcohol consumption (TAC) and the number of HDDs during treatment. TAC was assessed for patients who terminated the study. Since patients had to leave the study after the first relapse, the number of HDDs does not add much to the data and these findings are not reported. In addition to the outcomes measures mentioned in the protocol, we explored the following outcome variables: proportion of patients relapsed, proportion of patients continuously abstinent throughout the study period, cumulative abstinence duration, and drop-out rate

³Furthermore, DNA was collected and additional questionnaires measuring state anxiety, sleep quality, quality of life, drinking motives, personality traits, and drug and alcohol use were assessed at baseline, after four, and 16 weeks. Results are discussed elsewhere.

(Addolorato et al., 2007; Müller et al., 2015). Abstinence was defined as breath alcohol concentration of 0.00, negative self-report at every visit, and %CDT within a normal range at the end of the study. Drop-outs were defined as patients who terminated treatment before the end of the study due to other reasons than relapse. Other secondary outcomes included safety and tolerability of the study medication, changes in craving, anxiety, depression, and %CDT at the end of the high-dose phase.

2.7. Statistical analyses

Sample size was calculated based on a Log rank test of the difference in survival between two groups (high-dose versus placebo), with a power of 0.80 and two-tailed α of 0.05. Based on previous studies (Addolorato et al., 2002, 2007), a survival rate of 0.70 in the high-dose baclofen group and 0.45 in the placebo group was expected. A sample size of 64 patients per group was calculated (nQuery Advisor). The study was started with three groups (high-dose baclofen, low-dose baclofen, and placebo), but since the inclusion of patients went behind schedule, it was decided to stop the inclusion of patients in the low-dose baclofen group halfway through the study and to continue inclusion and randomization for the two extreme groups. Since power calculations were based on the difference in survival between the high-dose baclofen group and the placebo group, statistical power and the probability to find a truly existing effect was not affected.

Survival functions were estimated with the Kaplan-Meier approach, taking the first relapse as the event of interest. Subsequently, a Log-Rank test was used to test for group differences. Group differences in the proportion of patients that relapsed, the proportion of patients that were continuously abstinent, cumulative abstinence duration, and drop-out rate were tested with Chi-square tests or the non-parametric Kruskal-Wallis test. As a post-hoc analysis a dose-response effect was tested within the high-dose baclofen group, using a Cox-regression with dose as a predictor. Furthermore, a nonparametric Mann-Whitney test was used to compare the distribution of individual dosages in patients who relapsed or remained abstinent in the high-dose baclofen group. All analyses were performed separately for the high-dose phase (70 days) and for the complete medication period (112 days).

Changes over time in craving, level of anxiety, or depression were assessed with an ANOVA mixed model with time as the repeated measure, treatment group as a fixed factor, and the interaction between treatment group and time as indicator for the baclofen versus placebo effect. Analyses were done by intention to treat, counting pills every visit and assuming that patients took the drugs they were given (Lehert, 1992). All analyses were performed with SPSS Statistics version 22.

3. Results

The design and the patient flow of the trial is shown in Figure 1. Of 481 patients initially screened for the study between December 1, 2012 and August 31 2015, 157 patients were randomised. Six patients were not able to start with the medication due to medical reasons, resulting in 58 patients randomised to the high-dose baclofen treatment, 31 to the low-dose baclofen treatment, and 62 to the placebo group. Table 2 shows demographic and clinical characteristics of the included patients at baseline. There were no significant differences between groups at baseline.

Treatment adherence, which was defined as the number of dispensed pills minus the number of pills returned divided by the number of pills prescribed in the high-dose phase did not differ between groups ($\chi^2=3.79$, $df=2$, $p=0.15$). In the high-dose baclofen group a mean of 86% of the medication was taken as

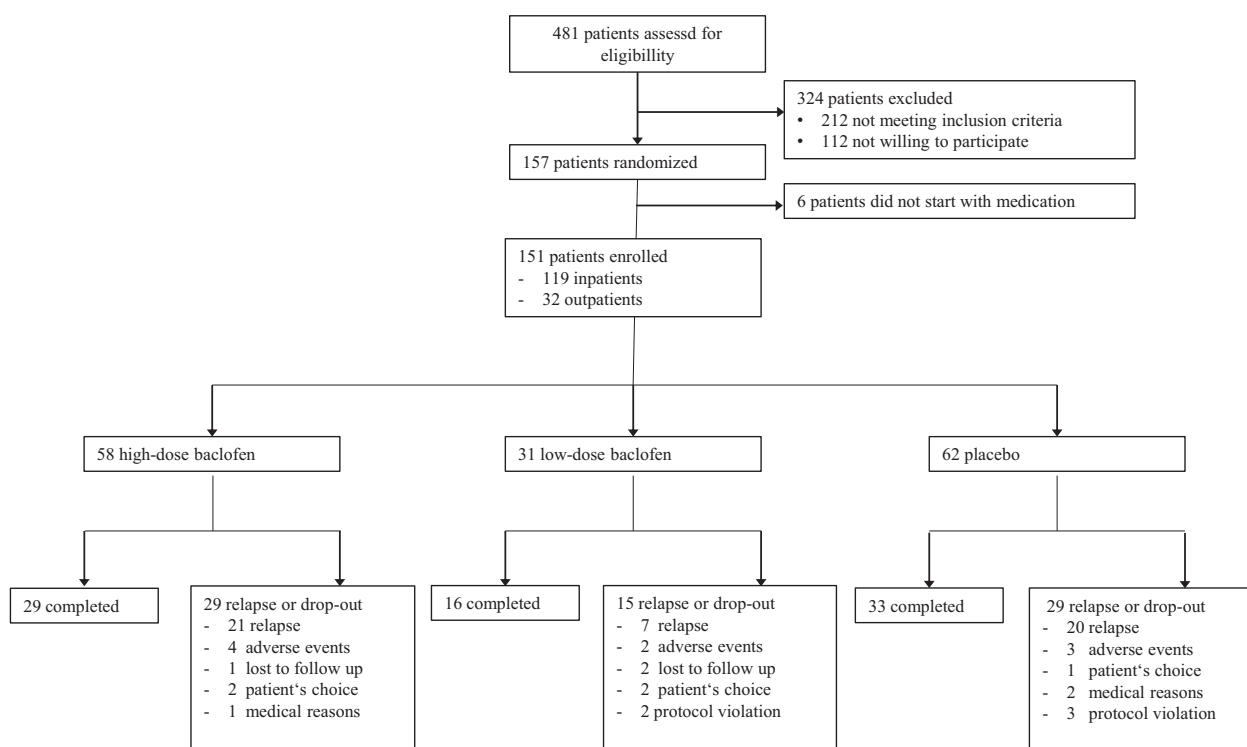


Figure 1 Trial profile.

prescribed, in the low-dose group 89% and in the placebo group 90%. Nine patients (15.5%) in the high-dose baclofen group reached the maximum dose (150 mg/day or 15 baclofen pills/day), compared to seven patients (22.6%) in the low-dose baclofen group (30 mg/day or 3 baclofen and 12 placebo pills/day), and 25 patients (40.3%) in the placebo group (15 placebo pills/day; $\chi^2=9.73$, $df=2$, $p=0.008$), with no significant difference between the high-dose and low-dose baclofen groups ($\chi^2=0.68$, $df=1$, $p=0.408$), and a significant difference between the baclofen and placebo groups ($\chi^2=9.23$, $df=1$, $p=0.002$). In the high-dose baclofen group, patients took a mean of 93.6 mg baclofen /day (SD=40.3).

The Kaplan-Meier survival analysis showed no differences between the three groups in the time to first relapse, neither for the high-dose phase ($\chi^2=0.41$, $df=2$, $p=0.813$), nor for the complete medication period ($\chi^2=0.04$, $df=2$, $p=0.982$; see Figure 2).

There were no group differences in TAC: high-dose baclofen group ($M=1.5$, $SD=4.3$), low-dose group ($M=1.3$, $SD=3.1$), placebo group ($M=0.9$, $SD=3.3$; $F(2,79)=0.76$, $p=0.473$). Concerning the proportion of patients that relapsed in the high-dose phase: high-dose baclofen group 11/40 (27.5%); low-dose baclofen group 4/20 (20.0%); and placebo group 11/44 (25.0%; $\chi^2=0.40$, $df=2$, $p=0.819$), no differences could be found. The results were comparable in the complete medication period: high-dose 29/58 (50.0%); low-dose 15/31 (48.4%); placebo 29/62 (46.8%; $\chi^2=0.13$, $df=2$, $p=0.939$). There were also no group differences in the proportion of patients remaining abstinent during the high-dose phase: high-dose 25/40 (62.5%); low-dose 13/20 (65%); placebo 29/44 (65.9%; $\chi^2=0.11$, $df=2$, $p=0.947$). Similar results were observed for the complete medication period: high-dose 25/58 (43.1%); low-dose 13/31 (41.9%); placebo 29/62 (46.8%; $\chi^2=0.26$, $df=2$, $p=0.879$). There

were no group differences in cumulative abstinence duration (days) in the high-dose phase: high-dose ($M=61.8$, $SD=16.5$); low-dose ($M=65.0$, $SD=11.1$); placebo ($M=62.1$, $SD=16.9$; $\chi^2=0.31$, $df=2$, $p=0.858$). Again, similar results were obtained for the complete medication period: high-dose ($M=79.5$, $SD=40.2$); low-dose ($M=75.8$, $SD=43.8$); placebo ($M=78.2$, $SD=41.9$; $\chi^2=0.21$, $df=2$, $p=0.902$). Drop-out rates did not differ between groups during the high-dose medication phase: high-dose 1/40 (2.5%); low-dose 2/20 (10.0%); placebo 1/44 (2.3%; $\chi^2=2.54$, $df=2$, $p=0.281$). Similar results were obtained for the complete medication period: high-dose 8/58 (13.8%); low-dose 8/31 (25.8%); placebo 9/62 (14.5%; $\chi^2=2.43$, $df=2$, $p=0.297$).

In a post-hoc analysis, the effect of the actual achieved maximum baclofen dose on survival time in the high-dose group was studied. In the high-dose phase no dose-response effect was found. However, for the complete medication period, Cox's regression analysis showed a significant hazard ratio of 0.99 (95% CI 0.98 - 1.0, $p=0.022$), suggesting that higher baclofen doses were associated with a longer time to first relapse. This was confirmed by the fact that the individual doses in the high-dose baclofen group were significantly lower in patients that relapsed ($M=84.8$ mg/day, $SD=6.9$) compared to patients that remained abstinent ($M=102.4$ mg/day, $SD=7.8$; $U=282$; $p=0.029$).

Table 3 shows all adverse events rated as moderate or severe for all treatment groups. There were frequent dose-related adverse events in terms of fatigue, sleepiness, and dry mouth with the highest frequency in the high-dose baclofen group (38%, 36%, 21%, respectively). Patients in the baclofen condition also reported more drowsiness and dizziness than those in the placebo group, but this effect was not dose-related. Compared with the combined low-dose baclofen and placebo group, patients in the high-dose

Table 2 Demographic and clinical characteristics of study participants at baseline.

	Total (N=151)	High-dose baclofen (N=58)	Low-dose baclofen (N=31)	Placebo (N=62)
Demographics				
Age (years)	44.8 (9.6)	45.8 (9.2)	44.7 (11.3)	44.0 (9.2)
Men	104 (68.9%)	41 (70.7%)	20 (64.5%)	43 (69.4%)
Married	82 (54.3%)	36 (62.1%)	17 (54.9%)	29 (46.8%)
Employed	88 (58.3%)	37 (63.8%)	18 (58.1%)	33 (53.2%)
Alcohol use				
Alcohol (gr/day)	141.8 (84.8)	147.0 (84.9)	132.5 (85.2)	141.7 (85.5)
Days abstinent	11.8 (4.4)	11.9 (4.7)	11.9 (4.3)	11.8 (4.3)
Duration of alcohol abuse (years)	19.5 (11.5)	18.8 (10.7)	21.5 (13.1)	19.0 (11.5)
Number of previous detoxifications	1.6 (2.8)	1.1 (1.6)	1.8 (2.9)	2.0 (3.6)
Questionnaires				
AUDIT	28.5 (5.1)	28.8 (5.2)	29.3 (6.1)	27.8 (4.5)
OCDS	29.4 (10.0)	28.2 (9.2)	29.5 (11.1)	30.4 (10.1)
BDI	19.6 (9.5)	19.6 (10.0)	22.0 (11.3)	18.2 (7.8)
STAI trait	49.8 (11.1)	49.7 (12.4)	52.1 (9.5)	48.6 (10.6)
Motivation	4.9 (0.4)	4.9 (0.2)	4.8 (0.6)	4.8 (0.5)
Biological measures				
Gamma GT	152.5 (198.6)	142.1 (269.5)	146.6 (215.1)	164.1 (356.1)
ALAT	50.2 (41.6)	45.3 (44.7)	49.1 (34.2)	54.7 (42.5)
ASAT	55.4 (50.4)	48.0 (42.0)	54.7 (55.1)	62.0 (54.2)
%CDT (baseline)	3.4 (2.5)	3.5 (2.6)	3.2 (3.1)	3.3 (2.3)
%CDT (end)	1.3 (0.5)	1.4 (0.6)	1.2 (0.4)	1.3 (0.3)

Data are mean (SD) or n (%). SD=standard drinks, AUDIT=Alcohol Use Disorder Identification Test, OCDS=Obsessive Compulsive Drinking Scale, BDI=Beck's Depression Inventory, STAI trait=Spielberger State-Trait Inventory, Gamma GT=gamma glutamyltransferase, ALAT=alanine amino transferase, ASAT=aspartate amino transferase, CDT=carbohydrate deficient transferrin

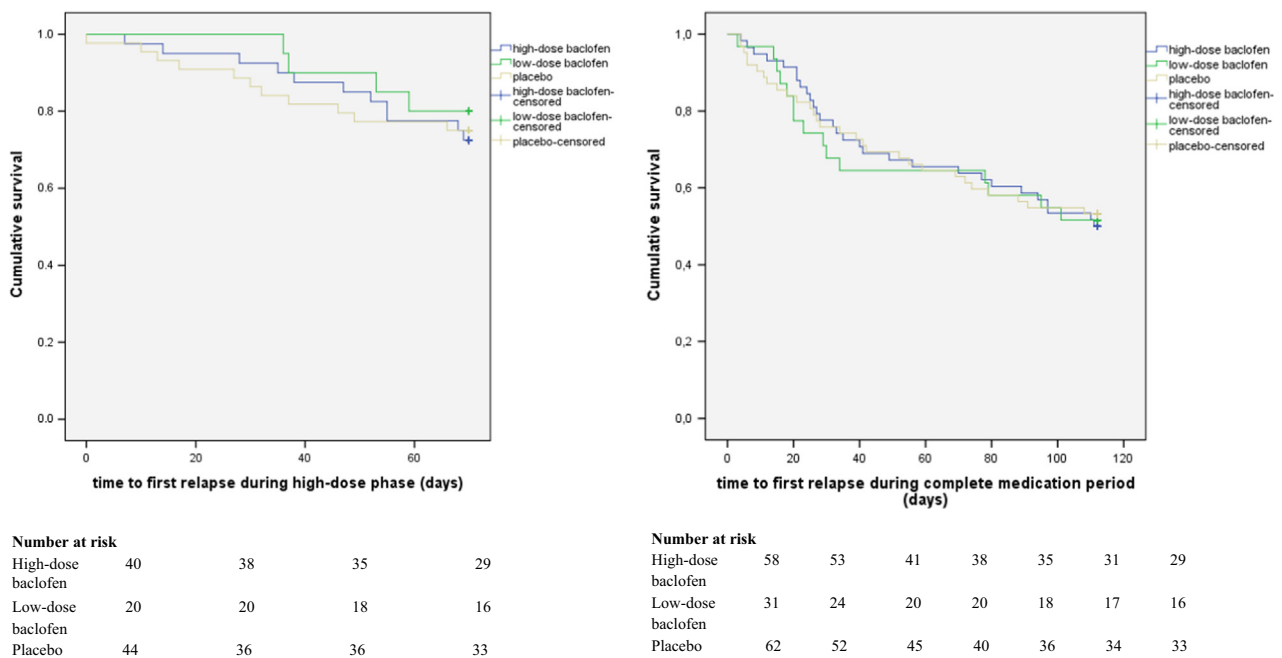


Figure 2 Kaplan-Meier survival curves for the high-dose phase and the whole medication period. Number of risk refers to the number of patients who did not relapse.

Table 3 Adverse events which occurred more than 10% and were rated as moderate or severe.

	Total (N= 151)	High-dose baclofen (N=58)	Low-dose baclofen (N=31)	Placebo (N= 62)
Adverse Event				
Fatigue	40 (26.5%)	22 (38.0%)	7 (22.6%)	11 (17.7%)
Sleepiness	40 (26.5%)	21 (36.2%)	8 (25.8%)	11 (17.7%)
Drowsiness	35 (23.2%)	17 (29.3%)	8 (25.8%)	10 (16.1%)
Dizziness	19 (12.6%)	11 (19.0%)	6 (19.4%)	2 (3.2%)
Dry mouth	15 (9.9%)	12 (20.7%)	2 (6.5%)	1 (1.6%)

Table 4 Changes in craving, trait anxiety, and depression from baseline till end of the study (16 weeks).

	Total (N= 151)	High-dose baclofen (N=58)	Low-dose baclofen (N=31)	Placebo (N= 62)
Craving (OCDS)				
Baseline	29.4 (10.0)	28.2 (9.2)	29.5 (11.1)	30.4 (10.1)
4 weeks	13.5 (5.5)	13.6 (5.8)	13.6 (5.8)	13.4 (5.1)
16 weeks	12.3 (5.0)	12.4 (4.9)	12.4 (6.4)	12.2 (4.3)
Trait anxiety (STAI)				
Baseline	49.8 (11.1)	49.7 (12.4)	52.1 (9.5)	48.6 (10.6)
4 weeks	39.0 (10.9)	39.3 (9.8)	39.3 (14.4)	38.5 (10.2)
16 weeks	38.5 (12.1)	37.3 (12.1)	42.2 (14.1)	38.0 (11.1)
Depression (BDI)				
Baseline	19.6 (9.5)	19.6 (10.0)	22.0 (11.3)	18.2 (7.8)
4 weeks	7.6 (6.9)	8.4 (8.2)	7.2 (5.9)	7.0 (5.9)
16 weeks	6.5 (7.7)	5.8 (7.3)	8.8 (10.5)	6.1 (6.6)

Data are mean (SD). OCDS=Obsessive Compulsive Drinking Scale, STAI trait= Spielberger State-Trait Inventory, BDI=Beck's Depression Inventory.

baclofen group showed significantly higher rates for fatigue ($\chi^2=6.33$, $df=1$, $p=0.012$), sleepiness ($\chi^2=4.57$, $df=1$, $p=0.033$), and dry mouth ($\chi^2=8.59$, $df=1$, $p=0.003$). In the high-dose baclofen group four patients stopped the study due to side effects (6.8%) compared to two patients in the low-dose baclofen group (6.5%) and three patients in the placebo group (4.8%; n.s.). One medication related serious adverse event occurred, when a patient in the high-dose group had to be hospitalized due to constipation.

Finally, a significant decrease in craving ($F(2,150)=191.01$; $p<0.0001$), trait anxiety ($F(2,152)=47.13$; $p<0.0001$), and depression ($F(2,152)=103.01$; $p<0.0001$) over time was observed, but no main effect of treatment (all p 's >0.438) and no interaction effect of treatment by time (all p 's >0.303) was found, indicating that these improvements cannot be attributed to the baclofen treatment (see Table 4). Furthermore, %CDT did not differ significantly between the groups at the end of the trial.

4. Discussion

The present study examined the efficacy of low- and high-dose baclofen treatment compared to placebo in patients with AD. No differences between the low-dose baclofen group, the high-dose baclofen group, or the placebo group

were found with regard to time to first relapse, proportion of patients that relapsed, proportion of patients continuously abstinent, cumulative abstinence duration, or drop-out rate. Furthermore, no effect of baclofen on craving, trait anxiety, or depression over time was observed. However, in line with previous studies (Addolorato et al., 2011; Ameisen, 2005; Bucknam, 2007), a (small) dose-response effect was found in the high-dose baclofen group for the complete medication period with higher doses being associated with a longer time to first relapse and higher doses in continuously abstinent compared to relapsed patients.

Our largely negative findings concerning the efficacy of high-dose baclofen in the treatment of AD are in clear contrast with the recent positive findings of Müller et al. (2015). Although there is the possibility that baclofen does not work and that the existing literature suffers from small study or publication bias, possible other reasons for this discrepancy are differences in (1) baclofen doses, (2) treatment setting and the amount and frequency of psychosocial support, and (3) the treated patient population.

In the study of Müller et al. (2015), the maximum dose was 270 mg/day and the mean dose was 180 mg/day, whereas in the present study the maximum dosage was 150 mg/day with a mean dosage of 94 mg/day. It is possible that many patients in our study were sub-optimally titrated and stopped at a relatively low dose. This interpretation is supported by our

(post-hoc) observation of a dose-response effect within the high-dose baclofen group. However, this effect was only evident in the complete medication period and there were no significant differences between the high-dose and the low-dose group. Furthermore, an additional post-hoc analysis was performed comparing patients with at least 120 mg baclofen per day ($N=23$) with those on placebo ($N=62$). Also these groups were not significantly different in their time to first relapse in the high-dose phase ($\text{HR}_{\text{adj}}=0.66$; 95% CI 0.20-2.11; $p=0.480$; for more details see [online Appendix](#)). Moreover, positive outcomes have been reported in the earlier low-dose (30-60 mg/day) baclofen studies ([Carter et al., 2009](#); [Colombo et al., 2003](#)), and no dose-effect relationship was observed in the study by [Müller et al. \(2015\)](#). Therefore, the explanation of our negative findings by suboptimal dosing should be regarded as tentative and needs confirmation in future dose finding studies. It should be noted, however, that in many patients, in the present study as well as in earlier studies ([de Beaurepaire, 2014](#); [Marsot and Imbert, 2014](#); [Müller et al., 2015](#)), it was not possible to reach higher baclofen dosages due to side effects, limiting the clinical feasibility of effective high-dose baclofen treatments.

Treatment setting and difference in psychosocial support could be another explanation for our negative findings. The majority of the patients in our study (119 out of 151) started their treatment as inpatients for at least 28 days, whereas patients in previous studies were only treated in an outpatient setting ([Addolorato et al., 2002, 2007](#); [Garbutt et al., 2010](#); [Müller et al., 2015](#)). As a consequence, many patients in our study followed an extensive psychosocial treatment during the baclofen trial, whereas in the studies with positive baclofen effects ([Addolorato et al., 2002, 2007](#); [Müller et al., 2015](#)), patients generally received a minimum of supportive therapy sessions. First, this might be a reason for lower overall doses in the present study, since patients and physicians might have been more sensitive to side effects in order to assure compliance with psychosocial therapy. Additionally, the absence of intensive psychosocial support in the study by [Müller et al. \(2015\)](#) may also explain the much higher relapse rates in their placebo group (70%) compared to ours (25%). Note that the relapse rates in the high-dose baclofen group were very comparable across the two studies: about 25% in the high-dose phase and about 55% in complete medication period. Therefore, it can be concluded that the outcome in the high-dose baclofen groups was comparable in both studies, and that the high response rate in our placebo group prevented the emergence of a significant medication effect. Altogether, these findings raise the possibility that baclofen does not add substantially to the effect of intensive inpatient treatment followed by a relatively high frequency of outpatient psychosocial aftercare; a conclusion that is consistent with previous findings regarding the efficacy of naltrexone in the treatment of AD ([Anton et al., 2006](#)).

Another possible explanation for the discrepancy between our study and the study of [Müller et al. \(2015\)](#) is that patients in our study consumed less alcohol before the start of the study (140 mg/day vs. 200 mg/day). In the discussion of their negative findings of low-dose baclofen, both [Garbutt et al. \(2010\)](#) (30 mg baclofen) and [Ponizovsky and Rosca \(2015\)](#) (50 mg baclofen) explicitly mention the possibility that their negative finding was due to their much

lower baseline alcohol consumption levels (about 70-80 mg/day) than those in the original low dose baclofen studies (about 180-200 mg/day) ([Carter et al., 2009](#); [Colombo et al., 2003](#)). The same phenomenon has been observed with other AD medications (e.g., nalmefene; [van den Brink and Aubin, 2013](#)) Maybe pharmacological interventions should be reserved for patients with more severe AD and/or higher drinking levels than those in the current study ([European Medicines Agency, 2011](#)). This may also have consequences for the most suitable treatment setting. In France, baclofen is broadly prescribed, including frequent prescriptions by general practitioners usually treating patients with relatively mild alcohol use disorders and relatively low alcohol consumption levels ([Blanken et al., 1994](#)), which might not be optimal.

Concerning safety and tolerability, we can conclude that most patients did not tolerate baclofen dosages over 100 mg/day and did not reach the maximal dosage. Furthermore, four patients in the high-dose group quit treatment due to side effects. The indication of a dose-dependent effect in the current study and the positive findings in the recent German study with higher doses ([Müller et al., 2015](#)), may indicate that our physicians and/or patients have been overly sensitive to side effects, and that at least for a subgroup of patients it may pay off to continue titration despite the occurrence of mild side effects. Note that side effects and drop-out due to side effects were equally frequent in the low- and the high-dose group (and more frequent than in the placebo group). Obviously, finding the optimal balance between ignoring and listening to side effects when increasing the dose may pose a major challenge for future clinical trials, and clinical applications. We experienced one serious adverse event related to the study medication, with one patient having to be treated for constipation. In line with previous studies ([Addolorato et al., 2002](#); [Müller et al., 2015](#)), we did not observe any signs of withdrawal when baclofen was reduced.

The current study has both strengths and limitations. The most important strengths are the study design, the sample size, and the structured assessments. However, the following limitations need to be considered. First, the study was conducted in different treatment centres, which could have caused measurement errors resulting in reduced statistical power. However, since the majority of patients were recruited from one treatment centre ($N=104$), we do not believe that this aspect can explain the negative results. Although the subpopulation of patients that started their treatment as an outpatient was relatively small, we found no indication that results differed for inpatients and outpatients. Second, in order to avoid patients to use baclofen and alcohol at the same time, patients who relapsed were removed from the study. However, since baclofen is known as an anti-craving agent, it would be of interest to assess drinking behaviour after the occurrence of a relapse in order to examine the efficacy of baclofen in reducing alcohol consumption, as is done in the on-going trials in France. Third, the duration of the present study was 16 weeks, with a high-dose phase of only 10 weeks. In order to draw conclusions about the long-term effects of baclofen in the treatment of this chronic, relapsing disorder, future studies are needed with a much longer treatment duration.

Fourth, in the present study medication adherence was assessed by pill count, since it is simple to perform, inexpensive, and non-invasive. However, this might not be an optimal measure since it does not confirm ingestion of the study medication. Therefore, in future studies other methods, such as tagging medications with PK measurements or electrical devices like 'aicure' should be considered. Fifth, no checks for 'unblinding' were conducted in order to know whether patients or clinicians were aware of treatment assignment. However, patients were seen by different clinicians during the inpatient and the outpatient period, which minimized the chance of an expectancy effect by clinicians. Moreover, if anything, unblinding generally results in an overestimation of the true treatment effect (Feys et al., 2014), which was absent anyway. Therefore, this issue seems hardly relevant in the interpretation of our findings.

In summary, the current study did not find evidence of a positive effect of either low or high doses of baclofen in AD patients. However, we cannot exclude the possibility that baclofen is an effective medication for the treatment of severe, heavy drinking AD patients not responding to or not accepting routine psychosocial interventions. So far, results from low- and high-dose baclofen studies in patients with AD are inconsistent with some positive studies (Addolorato et al., 2002, 2007; Müller et al., 2015) and some negative RCTs (Garbutt et al., 2010; current study). The findings of two completed, yet unpublished French trials, BACLOVILLE (clinicaltrials.gov: NCT01604330) and ALPADIR (clinicaltrials.gov: NCT01738282), testing doses up to 300 mg/day in a large number of participants have to be awaited. For the future, it is important to gain more insight in the mechanism of action of baclofen and to identify baclofen-responsive patients. For now, it seems that heavy-drinking AD patients, treated in a specialised outpatient setting with limited access or a lack of motivation for intensive psychotherapy might benefit most of a treatment with (high-dose) baclofen. Prescribing baclofen widely as it currently happens in France might be premature and should be reconsidered.

Contributors

EMB ES AG WvdB AB RWW contributed to study conception and design, supervision of the trial, data analysis, data interpretation and writing of the report.

EMB DdJ NS JWZ DvG PB TS contributed to patient recruitment, data collection, and review and approval of the report.

HD participated as independent physician.

MvT contributed to data analysis and data interpretation.

All authors contributed to and have approved the final manuscript. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest

All authors declare no support from any organisation for the submitted work. WvdB reports personal fees from Lundbeck, grants from Alkermes, personal fees from Pfizer, personal fees from Mundipharma, personal fees from Teva, personal fees from D&A Pharma, personal fees from Bioproject, personal fees from Reckitt

Benckiser/Indivior, personal fees from Novartis, outside the submitted work. RWW declares a speaker fee from Lundbeck, and, was co-applicant in two awarded grants from ERAB and was involved in the ERAB/ABMRF Underage Drinking Report (2012). ERAB is an independent foundation paid by the alcohol-industry that awards alcohol-related research after an independent scientific evaluation (peer-reviewed), with guarantee of completely independent scientific expression (in accordance with the Dublin principles). The other authors declare no conflicts of interest.

Acknowledgments

Funding for this study was provided by a private donation through the University of Amsterdam Fund (AUF 7344). We thank all patients for their participation in the study. Furthermore, we are grateful to all physicians and nurses of all treatment centres for their contribution. We also thank C Chmorikh and E Krediet, who assisted with the collection of the data.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.euroneuro.2016.10.006>.

References

- Addolorato, G., Caputo, F., Capristo, E., Domenicali, M., Bernardi, M., Janiri, L., Agabio, R., Colombo, G., Gessa, G.L., Gasbarrini, G., 2002. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomised controlled study. *Alcohol Alcohol.* 37, 504-508.
- Addolorato, G., Leggio, L., Ferrulli, A., Cardone, S., Bedogni, G., Caputo, F., Gasbarrini, G., Landolfi, R., 2011. Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomised, double-blind, placebo-controlled trial. *Alcohol Alcohol.* 46, 312-317.
- Addolorato, G., Leggio, L., Ferrulli, A., Cardone, S., Vonghia, L., Mirijello, A., Abenavoli, L., D'Angelo, C., Caputo, F., Zambon, A., Haber, P.S., Gasbarrini, G., 2007. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 370, 1915-1922.
- Ameisen, O., 2008. *The End of My Addiction*. Macmillan, New York.
- Ameisen, O., 2005. Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: a self-case report of a physician. *Alcohol Alcohol.* 40, 147-150.
- Anton, R.F., Moak, D.H., Latham, P., 1995. The obsessive compulsive drinking scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. *Alcohol. Clin. Exp. Res.* 19, 92-99.
- Anton, R.F., O'Malley, S.S., Ciraulo, D.A., Cisler, R.A., Couper, D., Donovan, D.M., Gastfriend, D.R., Hosking, J.D., Johnson, B.A., LoCastro, J.S., Longabaugh, R., Mason, B.J., Mattson, M.E., Miller, W.R., Pettinati, H.M., Randall, C.L., Swift, R., Weiss, R. D., Williams, L.D., Zweben, A., 2006. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomised controlled trial. *J. Am. Med. Assoc.* 295, 2003-2017.
- Beck, A., Ward, C., Mendelson, M., 1961. Beck depression inventory (BDI). *Arch. Gen. Psychiatry* 4, 561-571.
- Blanken, P., Hendriks, V., Pozzi, G., Tempesta, E., Hartgers, C., Koeter, M., 1994. *European Addiction Severity Index*, EuropASI.

- A Guide to Training and Administering EuropASI Interviews. EMCDDA, Lisbon.
- Bucknam, W., 2007. Suppression of symptoms of alcohol dependence and craving using high-dose baclofen. *Alcohol Alcohol.* 42, 158-160.
- Carter, L.P., Koek, W., France, C.P., 2009. Behavioral analyses of GHB: receptor mechanisms. *Pharmacol. Ther.* 121, 100-114.
- Chaignot, C., Weill, A., Ricordeau, P., Alla, F., 2015. Use in France of Baclofen for Alcohol Dependence from 2007 to 2013: cohort Study Based on the Databases SNIIRAM and PMSI. *Thérapie* 70, 443-453.
- Colombo, G., Vacca, G., Serra, S., Brunetti, G., Carai, M. a M., Gessa, G.L., 2003. Baclofen suppresses motivation to consume alcohol in rats. *Psychopharmacology* 167, 221-224.
- Davidoff, R.A., 1985. Antispasticity drugs: mechanisms of action. *Ann. Neurol.* 17, 107-116.
- de Beaurepaire, R., 2014. The use of very high-doses of baclofen for the treatment of alcohol-dependence: a case series. *Front. Psychiatry* 5, 143.
- European Medicines Agency, 2011. Annual Report of the European Medicines Agency 2010. European Medicines Agency, London.
- Feys, F., Bekkering, G.E., Singh, K., Devroey, D., 2014. Do randomised clinical trials with inadequate blinding report enhanced placebo effects for intervention groups and nocebo effects for placebo groups? *Syst. Rev.* 3, 1-14.
- Flannery, B.A., Volpicelli, J.R., Pettinati, H.M., 1999. Psychometric properties of the Penn alcohol craving scale. *Alcohol. Clin. Exp. Res.* 23, 1289-1295.
- Garbutt, J.C., Kampov-Polevoy, A.B., Gallop, R., Kalka-Juhl, L., Flannery, B.A., 2010. Efficacy and safety of baclofen for alcohol dependence: a randomised, double-blind, placebo-controlled trial. *Alcohol. Clin. Exp. Res.* 34, 1849-1857.
- Koob, G., Volkow, N., 2010. Neurocircuitry of addiction. *Neuropsychopharmacology* 35, 217-238.
- Lehert, P., 1992. Review and discussion of statistical analysis of controlled clinical trials in alcoholism. *Alcohol Alcohol.* 157-163.
- Marsot, A., Imbert, B., 2014. High variability in the exposure of baclofen in alcohol-dependent patients. *Alcohol. Clin. Exp. Res.* 38, 316-321.
- Müller, C.A., Geisel, O., Pelz, P., Higl, V., Krüger, J., Stickel, A., Beck, A., Wernecke, K.-D., Hellweg, R., Heinz, A., 2015. High-dose baclofen for the treatment of alcohol dependence (BACLAD study): a randomised, placebo-controlled trial. *Eur. Neuropsychopharmacol.* 25, 1167-1177.
- Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695-699.
- Ponizovsky, A., Rosca, P., 2015. Baclofen as add-on to standard psychosocial treatment for alcohol dependence: a randomised, double-blind, placebo-controlled trial with 1year follow-up. *J. Subst. Abus. Treat.* 52, 24-30.
- Rehm, J., Shield, K.D., Gmel, G., Rehm, M.X., Frick, U., 2013. Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *Eur. Neuropsychopharmacol.* 23, 89-97.
- Rief, W., Glombiewski, J.A., Barsky, A.J., 2009. Generic assessment of side effects: GASE. www.GASE-scale.com.
- Saunders, J., Aasland, O., Barbor, T., De La Fuente, J., Grant, M., 1993. Development of the alcohol use disorders identification test (AUDIT). WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction* 88, 791-804.
- Sheehan, D., Lecrubier, Y., Sheehan, K., Amorim, P., Janavs, J., Weiller, E., Dunbar, G., 1998. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* 59, 22-23.
- Sobell, L.C., Sobell, M.B., 1992. Timeline follow-back, In: *Measuring alcohol consumption*. Humana Press, 41-72.
- Spielberger, C.D., 2010. *State-Trait Anxiety Inventory*. Wiley & Sons, New York.
- van den Brink, W., 2012. Evidence-based pharmacological treatment of substance use disorders and pathological gambling. *Curr. Drug Abus. Rev.* 5, 3-31.
- van den Brink, W., Aubin, H., 2013. Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: results from a subgroup analysis of two randomised controlled 6-month studies. *Alcohol Alcohol.* 48, 570-578.
- World Health Organization, 2014. *Global status report on alcohol and health*.